Technology, public policy and control of transboundary livestock diseases in our lifetimes

R.G. Breeze

Centaur Science Group, 1513 28th St NW, Washington, DC 20007 United States of America

Summary

There are no technological barriers to eliminating major transboundary livestock diseases. 'Elimination' means that diseases no longer threaten livestock in the developed world nor the livelihoods of hundreds of millions of small farmers elsewhere. The problem is not lack of technology but failure of public policy. Developed country policy should actively combat accidental and intentional introductions; protect livestock against future advanced biological weapons; minimise the economic impacts after introduction by any means; abandon mass slaughter as a control tool; engage in disease removal in pursuit of a global economic, societal, and environmental agenda; and make appropriate national and cooperative investments. This is the moment for policy change because transboundary livestock disease elimination now involves powerful government ministries outside ministries of agriculture that are concerned about disease threats from many sources. Change can acquire support from the public and many organisations with shared interests. New policy is needed to change the belief that government is solely responsible for excluding disease, responding to introductions, and compensating farmers for losses during eradication. Effective border control and domestic preparedness programmes depend upon government and industry working together with costs falling upon those responsible in the form of 'user fees'. Compensation for stock slaughtered during outbreak control should be covered by private insurance. Government and industry should share the costs of an effective surveillance, diagnostic and response system. Surveillance must achieve or approach real-time understanding of the disease situation at all stages and in all places and be accessible over the Internet by diverse government agencies and stakeholders in-country and abroad. Traditional responses must be abandoned because they encourage terrorism. Regulatory approval processes must be modernized because they cannot keep up with new technology.

Keywords

Command, control and communication system — Electronic disease reporting system — Especially dangerous pathogen — New technology — Outbreak insurance — Polymerase chain reaction — Responsibility — Slaughter policy — Surveillance — Threat agent detection and response — Transboundary disease — Vaccination.

Introduction

There are no technological barriers to the elimination of the major transboundary livestock diseases in our lifetimes. Here, these diseases are defined as transmissible diseases that have the potential for very serious and rapid spread, irrespective of national borders; that are of serious socio-economic or public health consequence; and that are of major importance in the international trade of animals and animal products. It was this type of disease that was included among the former List A diseases of the World Organisation for Animal Health (OIE). 'Elimination' means a condition where diseases no longer threaten the flocks and herds of the developed world or the livelihoods of hundreds of millions of small farmers elsewhere. For some

diseases 'elimination' may not be the same as eradication because reservoirs of potential infection may persist, but if we commit to a new vision, eradication of many diseases will occur during the lifetime of our children. This is not incredible: in 1885 Louis Pasteur tested his rabies vaccine in man for the first time; in 1983 trials of a vaccine for foxes and other wild animals began in Germany and now many countries are rabies-free.

Technology always gets better over time and that of the future will certainly be better than that of today, but what we have now is good enough to remove the threat of transboundary diseases. The problem today is not lack of technology but failure of public policy. Developed countries, such as the United States of America (USA), Canada, Western European countries (including to some extent Russia), Japan, Australia and New Zealand, have strong veterinary infrastructures, financial resources and the technology but do not have the diseases. The rest of the world has the diseases but not the infrastructure, resources or technology. Public policy in our world frames the threat in agricultural terms and focuses almost entirely on the domestic consequences to agriculture of periodic disease introductions in the course of international travel and trade - and, most recently, deliberate introductions by terrorists. With this policy, the threat continues to exist and with the increasing complexity of agribusiness and globalisation, the potential consequences grow ever more severe.

The policy that the countries of the developed world should adopt is quite simple and is shaped entirely by the realisation that for these countries transboundary livestock diseases are not a mere domestic agricultural matter: they impact national security, and undermine international commitments to world trade, economic development, alleviation of poverty, environmental stewardship, international public health, animal welfare and wildlife conservation. Developed countries must commit to:

- a) actively combat accidental disease/pathogen introduction and deliberate attack by terrorists
- b) protect livestock against advanced biological weapons (BW) of the future
- c) minimise the economic impacts after introduction by any means
- d) abandon mass slaughter as a control tool
- c) engage in disease removal in pursuit of a global economic, societal, and environmental agenda
- f) make appropriate national and cooperative investments to effect this policy.

So why does such a policy not exist? The main reason is the mistaken belief among policymakers, agricultural and other stakeholders and the public that the current policy is based upon the limitations of the very best science available in the world today. Science generally does allow novel solutions for old and intractable problems and shapes new policy to exploit these to the maximum. But this is not true of the field of transboundary disease control.

Safe and effective foot and mouth disease (FMD) vaccine has been available for over 40 years, but its use in the developed world to respond to accidental or deliberate disease introductions is not policy because of the fact, despite the reality of successful vaccination programmes in Europe and South America, that a few vaccinated cattle that are also exposed to infection may persistently carry virus in their throats and are suspected to be a source of infection to others. Compounding this was the absence, until 1995, of any means to distinguish between vaccinated animals and those that had recovered from infection (including those that had been both vaccinated and infected). For these reasons, vaccine was not used to assist control of FMD infection in Great Britain in 1967 or in 2001 - and would still not be used in Great Britain (or the USA) in 2006.

Between 1966 and 2006, a conservative estimate puts government spending in Europe, Russia, North and South America, South Africa and Australia at over US\$ 1 billion on the construction and operation of specialised laboratory facilities, and on the salaries, equipment, supplies and operations of those researching FMD. But this investment has had no impact whatsoever on disease control. This is not just a British problem or limited to FMD: in the USA in 2006 there is not a single transboundary disease for which the federal government is ready and able to vaccinate any relevant proportion of the livestock or poultry at risk. This would suggest an extraordinary and sustained failure of science - the absence of any return on public investment on six continents over 40 years through any discovery that might permit use of vaccine and drive new policy. In fact there were such discoveries - they were just not adopted by veterinary regulatory agencies. The failure was in policy.

Present: scientist-enabled policy

The established relationship between science and policy for transboundary livestock disease control is shown in Figure 1. This does not reflect all the scientific inputs that might be brought to bear but just those sufficient for policymakers. The pool of transboundary animal disease workers is small and most are employed in non-policy positions by the same government agencies charged with either research or diagnosis and with determining and implementing the control policy. This cadre is weakly placed bureaucratically and in the long shadow of a dominating historical dogma — that for almost 300 years slaughter has been the policy. It is virtually impossible for

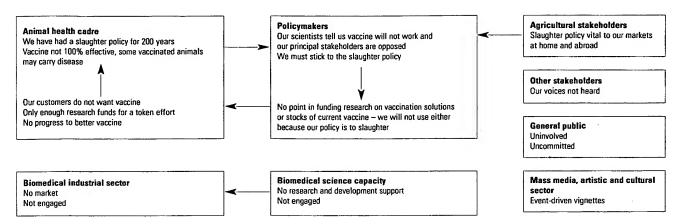


Fig. 1
The scientist-enabled policy cycle for transboundary livestock disease control

them to challenge the prevailing orthodoxy and completely so by making arcane comments and caveats about the technical properties of present or future vaccines and how these might influence some future event that is itself uncertain.

Policymakers lose no support from their strongest agricultural stakeholders by sticking with the status quo and what they hear is their scientific experts telling them there might be problems because of vaccine uncertainties. There is no gain for either policymakers or agricultural stakeholders in preparing for future uncertain events that have no political constituencies when there are plenty of current and certain problems that do. And agricultural stakeholders hold that a slaughter policy at home is vital to their markets domestically and overseas. So slaughter remains the policy.

Any broader discussion outside the Ministry of Agriculture does not occur, because the national biomedical sectors are not sufficiently knowledgeable of the issues and remain unengaged because there is no opportunity for reward. The general public is unaware, uninvolved and uncommitted. Even the sparks that the mass media and the artistic and cultural sector can ignite to sway public opinion and shift the most ossified bureaucracies are few, because they are generally struck by the rare events in their home countries that only happen every 30 years or so; the true calamity occurs in developing countries every day, but this is not widely reported by the media in developed countries.

The end result of all these factors is that policymakers believe there is no point in funding research on vaccination solutions or even in stockpiling enough of the current vaccine to make a difference when catastrophe strikes.

New: policy-driven science

What is needed is policy-driven science, where the policy is based upon a bold vision of the future, effective leadership across many countries and sectors, skilled advocacy and committed, zealous supporters, all of which will have to be sustained for a generation.

Time has conspired to move the issue of transboundary livestock disease elimination outside the confines of the world's Ministries of Agriculture and into a nexus with the more powerful realms of Defence, Foreign Affairs, Public Health, Homeland Security, Justice, Commerce, and Finance. Today, Ministries of Agriculture are not powerful within governments and the elimination of major livestock diseases will only be possible with the commitment of those ministries that are motivated by the following factors:

- a) globalisation is not just an economic matter of shipping vast amounts of manufactured goods halfway round the world from where they can be produced most cheaply to places from which services, finance and high technology products can be sent in return. With this commercial torrent from far away lands comes crime, terrorism, and all the diseases that flourish in crowded places where there are no basic public health, veterinary or environmental services, and clean water, sewage treatment and the fundamentals of sanitation are unknown;
- b) the crumbling residue of offensive BW research and production programmes across the former Soviet Union and in other countries poses a clear and present danger;
- c) governments in many parts of the world are in a protracted struggle with resourceful and well-funded terrorist groups;

d) the scientist-enabled policy that has killed countless millions of healthy livestock is now killing millions of poultry as avian influenza (AI) H5N1 continues to spread westwards. Now there is a national and international crisis: billions of dollars have been pledged to domestic preparedness in public health agencies and the military, and billions more have been raised internationally to take the fight to the epicentre in Asia. If a small fraction of this money can establish effective veterinary infrastructure and safe animal agricultural practices in that region, this will be the basis for dramatic future improvements for all diseases.

The simple policy that is needed was stated earlier and is shown in Figure 2. The first step for its implementation is for policymakers to ask the entire scientific community and industry four key questions: what science can be applied to achieve these goals now; what science must be developed in the future; what is the estimated cost; and what are the constraints? The community will be eager to become informed and engaged because the potential individual rewards are obvious. The result should be a research and development agenda that covers the ground from basic research to veterinary and agricultural production practice and that identifies the critical path to product development and manufacturing through the government and private sectors. This is not difficult.

Informed public support

A key responsibility of government is to fund the research and development, and reduction to practice. But governments cannot do this in a vacuum – it is very much easier if the issue is perceived as important by the general public and supported and sustained over time by the many special interest groups who have the organisational power and advocacy skills to promote, or obstruct, key elements or all of the policy. Visible scientific outcomes that

regularly demonstrate progress towards goals and reinforce both accomplishment and national commitment are also powerful motivators. Traditional agricultural stakeholders will find much that is attractive in a new approach to disease control: their fears will not be of the policy itself, only of who is to pay for it. Supporters will be found among those groups and individuals concerned about one or more of the following:

- the environment at home and abroad
- poverty reduction and improved public health in developing countries, especially Africa
- global economic development and its international health consequences
- animal welfare at home and abroad
- the conservation of wildlife and their habitats.

Support can also be obtained from the mass media and the artistic and cultural sectors – highly influential groups whose potential contributions have been almost totally overlooked in the past except at times of national crisis.

Many societies are growing more distant from the living sources of their food. Fifty years ago, most people were still in regular contact with those who grew, processed or delivered their food, and oftentimes with the livestock and poultry too. The growth of supermarkets in the developed world abolished these connections and for most people their first contact with their food is when they see cuts of meat, boxes of eggs or piles of fresh produce in the food aisles. Later came prepared foods ready to be cooked at home. Now the entire meal for a family may be in a box that just needs reheating. When the consequences of FMD control are shown on the television news as we eat these meals, the event could be taking place on another continent, even with the plumes of smoke outside and the

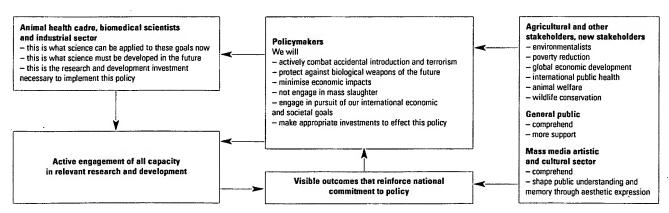


Fig. 2
The policy-driven science cycle for transboundary livestock disease control

fires on distant hillsides. A critical shift in public opinion will occur once the importance of transboundary livestock disease elimination can be effectively communicated.

The story of transboundary livestock diseases has not yet been told, but when it is this will generate the public support to solve the pressing problems that are now engaging government ministries in many countries. Peter Roeder, a Food and Agriculture Organization (FAO) Field Officer, summed it up well in a June 2001 letter to The Times of London published at the height of the British FMD epidemic, in which he described the effects of FMD in various parts of the world: 'the Cambodian subsistence farming family loses half its rice crop when the buffaloes are hit during paddy field preparation, and the fattening pigs and calves die or require expensive treatment. The progressive Bangladeshi dairy farmer with ten cows loses overnight most of the milk production and daily income from it. When the disease strikes just after lambing time, the northern Iraqi shepherd loses 400 of his 500 lambs from heart damage, together with much of the milk for consumption and sale. These real examples do not cover the full spectrum of impact, but they do illustrate the immediate, direct effects of FMD. The fight against epidemic diseases of humans and animals is far from over; indeed, for livestock diseases it has barely started in most of the world. A concerted fight against FMD and other epidemic diseases is needed, to start at their source where the reservoirs of infection persist. For the more developed nations to assist the developing nations in this fight must be regarded as enlightened self-interest, not benevolence'.

We cannot tell this story through government technical reports. To accomplish a policy change we must solicit the input of creative artists who can tell the story in ways that reach all the audiences that matter.

Challenging the dogmas

The prevailing wisdom is that it is the responsibility of government to keep transboundary livestock diseases out of our countries: when government fails in this task it is again government's responsibility to control the ensuing disease outbreak and compensate farmers whose livestock have been seized and killed in the process. Intermittent disease introductions are regarded as inevitable 'acts of God' that could not have been deflected by any reasonable human effort beforehand and for which no one can be held accountable. In this scenario, efforts to control disease outbreaks are framed in terms of a 'War against FMD' - in which FMD is the villain, farmers are innocent victims and the government seeks to be the hero (9). Livestock owners and agricultural industries are largely passive bystanders. The general public is not involved except as the intended audience for displays of government competence and as the source of tax revenues to support the whole enterprise, including compensation.

The author rejects this prevailing wisdom and sets out another view below. This is needed because the whole power of technology lies not in the invention itself but in how it is used. Success depends upon government and industry working together in a process that is comprehensive, adequately funded, and performing to measurable benchmarks, with costs falling upon those responsible in the form of 'user fees', not the general public through tax revenues. Specifically, there should be no government compensation of livestock owners for stock slaughtered during outbreak control: this should be covered by private insurance. Compensation for animals slaughtered during disease epidemics was a concept introduced over 100 years ago to encourage reporting by owners. While it may have some utility in this regard, and certainly still in developing countries, any benefit is greatly outweighed by the fact that it encourages and enables livestock owners and the industry to be disengaged from the entire issue of transboundary livestock disease control at the international, national and local levels, even down to the biosecurity of their own premises. This is a fatal weakness.

Roles and responsibilities

For the purposes of this paper, 'industry' means those concerned with the raising, processing and sale of livestock and poultry from farm to fork, including all zoo and commercial animals and birds from which commerce or profit is derived regardless of species. Other private sector industries will be identified later. The comments are directed at all transboundary livestock disease threats, with FMD as the example: one cannot detail all possibilities here.

Government and industry must agree on effective border control

Foot and mouth disease is not endemic in many countries, e.g. North America and Western Europe, so the only way FMD virus can become a livestock problem is if someone accidentally or deliberately brings in live infected animals, infected animal products, or the virus itself. The industry has no powers to prevent accidental or deliberate FMD introduction – this is an 'essentially governmental function' (although government employees do not necessarily have to perform the function). Governments can fulfil this responsibility by introducing legislation that covers the following elements:

a) the costs of preventing FMD and other transboundary livestock diseases from entering a country should primarily be borne by those passing across the country's borders or importing animals or goods of any kind that might carry

these infections. Globalisation has created a torrent of goods and people moving quickly across international borders and over vast distances and all involved in this torrent should contribute towards its effective policing;

- b) plans should be developed for effective screening of people, conveyances (cars, trucks, boats, planes) and goods of all kinds arriving in a country to ensure that illegal imports of animals and animal products that might carry transboundary livestock diseases are detected;
- c) systems to track and validate the movements of people, conveyances and goods should be employed to identify those arriving from countries where transboundary livestock diseases occur. Those identified conveyances and their contents and goods should be unalterable from the point of origin and they should be capable of being validated at the point of entry to counter criminal activity exploiting globalisation;
- d) performance benchmarks should be established for issues such as how higher risk traffic will be identified and intercepted; what proportions of passengers, conveyances and goods will be examined; how they will be examined; and how results will be reported. So far as possible, robotic automated devices should be employed to screen the maximum numbers of potential targets. Industry must accept that it is not possible to examine all travellers, goods or conveyances and must agree with government what an acceptable fraction should be. Later, there might be redirection of inspection resources based upon risk assessment and experience;
- e) a greater proportion of travellers, containers and goods coming from countries in which FMD and other diseases of concern are known to be present should be examined than from disease-free countries, thereby encouraging countries to eliminate disease within their borders. All travellers, conveyances and goods from countries not making acceptable progress in transboundary livestock disease control should be inspected, regardless of delays at the point of entry thus elevating livestock disease from merely an agricultural problem at home to one that catches the attention of the whole economy;
- f) a fee should be assessed on all travellers, conveyances, shipping containers and goods entering a country to pay for an agreed share of the increased costs of inspection and the costs of transboundary livestock disease elimination overseas. This fee would be greater for conveyances carrying live animals or animal products and for imports of live animals and animal products but inspection should not be restricted only to these since the declared manifest might be incorrect. Reduced fees might apply to those meeting higher standards of validation as to the nature of the import and country of origin;
- g) all sector components should contribute the shipping companies as well as the shipper to ensure that all are

vested in the outcome. There should be real and significant penalties on the boat, truck or airline industry members found to be knowingly or unknowingly carrying illegal imports to discourage illegal imports at the point of loading in a foreign country;

- h) on a non-disclosure basis, the government should make available to industry representatives up-to-date records on how well performance benchmarks are being met. The government should have the necessary resources to meet these benchmarks from tax revenues and user fees and be prepared to demonstrate that it is meeting its performance promises;
- i) laws and regulations on penalties for failing to comply with importation requirements should be reviewed to ensure that penalties are commensurate with the likely degree of economic consequence;
- j) through differential fees, the government should encourage adoption of importation practices that minimise fraud and maximise effective inspection, such as source validation, unalterable product seals, electronically verifiable certificates of origin, and lifetime tracking of the imported products in ways that can be validated in real time by customs inspectors at the point of importation. Specifically, there should be biological tests to validate the declared region or country of origin of meat that can be conducted at the point of importation.

Some of the steps above will deter terrorist attack using transboundary disease agents illegally brought into the country. Additional border control measures to deter terrorism benefit all society and are properly borne by general tax funds, not travellers and importers. The purpose of the above elements is to ensure that all those engaged in entering a country, with and without products or animals that might carry infection, contribute towards the costs of an effective programme that has a measurable impact on preventing illegal importations and ultimately on eliminating the sources of transboundary livestock diseases. The above comments do not address deliberate introduction (see below).

Government and industry must be accountable for performance

Governments have chosen to retain all powers to: diagnose FMD and other transboundary livestock diseases; respond to an introduction by vaccination and other health interventions; and to release vaccine to livestock owners. Industry should share the costs of an agreed and effective diagnostic and response system in which government meets agreed performance benchmarks that will limit industry losses should FMD occur. The elements of such a system are the same for both accidental and deliberate disease introductions. They are as follows (the term

'livestock' also includes all forms of zoo, game and other non-farm animals and birds):

- a) early reporting of suspicious cases is critical to limiting any subsequent epidemic. Through education and training, government should ensure that livestock owners and those employed in the industry know what to look out for and how to report suspicious cases;
- b) an inducement scheme might be adopted to encourage reporting. This component should have performance benchmarks;
- c) within 6 h of the reporting of a suspicious case, government should have made a definitive detection of the transboundary livestock disease by transporting samples to a national or regional laboratory or by detection on the farm. This component should have performance benchmarks:
- d) in cooperation with industry and the authority or authorities regulating the practice of veterinary medicine, government should have in place an emergency communications capability to inform directly all livestock owners and veterinarians, or a relevant defined subset of them, immediately (within 1 h) after a definitive diagnosis on a 24 h, seven days a week basis. This communication system may be by telephone, email, pager or other electronic means. This component should have performance benchmarks;
- e) through education and training, government should ensure that all livestock owners and veterinarians know what preventative measures they should employ under their farming or business circumstances when disease is diagnosed. This component should have performance benchmarks. It is unrealistic to expect that all the industry will remain in a state of high alert on a permanent basis. But it is not unrealistic to expect that given a timely and specific alarm they should be able to respond immediately and appropriately based on their specific situation;
- f) within 24 h of reporting, government should have made a definitive diagnosis, have determined the strain or subtype of the pathogen, and ordered the production and distribution of the most efficacious vaccine from stockpiled antigens. This component should have performance benchmarks;
- g) the government should maintain a stockpile of vaccines (in the form of frozen antigen or other formulations of indefinite shelf life) to protect the country's livestock against all strains of the pathogen circulating in the world. The numbers of doses of each vaccine may not be the same as the total number of susceptible animals or birds but the government shall fully compensate, for all direct and indirect losses, all owners for whom vaccine is not available in the event of an outbreak:
- h) the government should have a plan and capability to deliver sufficient vaccine for all susceptible livestock to

- their owners at pre-determined collection points (not at the farm) starting 72 h after definitive diagnosis and being complete within 144 h to 168 h so that the national herds and flocks have all been vaccinated within seven to ten days after detection. This component should have performance benchmarks;
- i) owners should know where to collect their vaccine supplies, how to implement farm biosecurity measures and how to vaccinate their livestock or poultry. This will require significant advance emergency planning and regular exercising;
- j) stockpiling vaccine precursors and the subsequent process of vaccine production and nationwide distribution under time deadlines are functions which would be best accomplished by the private sector using the principles already in place by which express mail companies provide integrated warehousing, distribution and delivery for other industrial sectors;
- *k*) the government should ensure that sufficient laboratory capability and capacity exist to perform all diagnostic and differential diagnostic tests during and after an outbreak in a timely manner to meet performance benchmarks;
- l) regional Agricultural Response Teams, such as the state response teams in the USA, should be established, trained and exercised (more information about the US model is available at http://www.flsart.org/). These teams should bring all the relevant national and regional government and private sector resources to bear in any form of agricultural emergency;
- m) all components of the livestock production and animal product processing industry and the retail sector should pay a share of the above costs not borne by government because all components benefit from animal agriculture this includes auctions, retail stores and slaughter plants. The consumers' portion is paid by government tax revenues. The purpose of such a cost-sharing scheme is to ensure that all those benefiting from the production, processing or sale of animals and animal products of national origin and those similarly benefiting from imported animals or animal products contribute towards the costs of an effective programme for the earliest possible detection and most rapid effective response to transboundary livestock disease threats and are actively engaged in their part of such a programme should disease occur:
- n) when a transboundary livestock disease outbreak occurs during a period in which the government is not meeting its performance benchmarks for importation security, the industry should not have to pay its share of disease control costs stemming from failure on the government's part;
- o) the same conditions will apply when there is a government failure in regard to diagnosis, vaccine deployment and preparedness;

p) the first owner to report a suspicious case that proves to be a transboundary livestock disease should be rewarded by government at four times the value of the stock; those subsequently reporting suspicious cases (that prove positive) within the first two weeks after the definitive diagnosis should be rewarded at twice the value of the stock. This is a reward for prompt notification, not a form of compensation for livestock killed in the course of control:

q) it is assumed that the national flocks and herds would be vaccinated within 14 days of first detection (13 days after definitive diagnosis). In the first 14 days, flocks and herds could be slaughtered as part of the control measures: thereafter, the numbers of infected premises should be small as vaccination and biosecurity measures take hold. Government would not pay compensation for any livestock killed during control measures: government should ensure that livestock owners can obtain insurance in advance against such an eventuality.

These elements are intended to promote industry-wide vigilance and immediate diligent attention and response after disease is diagnosed. With all performance benchmarks met, by government and industry, the goal is to halt an outbreak within two weeks of diagnosis by active commitment of all sections of the industry and related industries.

There are no acts of God

Once upon a time the only explanation for catastrophic disasters with extensive loss of human and animal life, e.g. hurricanes, floods, intense heat waves, droughts and other weather related events, was that these were acts of God beyond human control. The same explanation held for epidemics of infectious disease in humans and animals, such as the Black Death and the eruption of rinderpest into Europe. Now we know differently. While the natural event must necessarily run its course, advanced planning and preparedness can greatly mitigate the consequences. The same is true for incursions of transboundary diseases. Authorities must expect that exclusion procedures will sometimes fail and preparedness planning must assume this. When an accidental disease introduction results in a widespread livestock disease epidemic this represents two failures - in exclusion and in preparedness. It is not sufficient to point out that other countries have suffered through similar debacles. Either the government's Chief Veterinarian gave poor advice and must be held accountable or the government ignored good advice and is itself responsible.

The veterinary profession must make a stand on animal welfare

In a recent report to the European Food Safety Agency (5) an Expert Scientific Group stated: 'The eradication of FMD

often involves killing of animals, sometimes in huge numbers and under less than ideal conditions...Poor welfare can result from inadequate stunning and might lead to pain from the injuries and from killing that is not instantaneous. There may also be other logistical problems, such as crowding resulting from pressure of time and space and restrictions on movements of stock, which can be causes of poor welfare'. The author would put the case less delicately. The mass killing in Great Britain in 2001 was the most shameful episode in the history of British Veterinary Medicine and today's images of thousands of bags of poultry being buried alive or hurled struggling onto the flames to control AI would be like a vision from Medieval Europe were it not for the fact that the bags are plastic and the perpetrators are wearing the latest personal protective equipment. How have we got to this place? In fact, we should not be engaged in mass killing at all: a non-slaughter alternative was available for FMD in 2001 and would be available for AI today if policymakers had acted in 1998. It is past time for the veterinary profession and its regulatory bodies to take a stand in regard to mass animal slaughter.

The potential for real-time disease surveillance

The pattern of events in the world, whether an infectious disease or criminal activity, commonly turns on three characteristics: complexity, venues and time. In the case of each transboundary livestock disease, the global pattern of events from places where the disease exists through the streams of travel and commerce that take it to our countries and what happens there when disease erupts can be described by these three characteristics, as follows:

- a) Complexity complexity of nonlinear systems is a way of understanding (8) the relationship among things that interact, such as the organisation of agriculture (including small and subsistence farmers) in the countries of disease origin and of global agribusiness in 2006
- b) Venues when discussing transboundary disease the venues to consider are:
- physical world: the farms and fixed assets of global animal agriculture and agribusiness and the flows between them, e.g. digital geographic information systems (GIS) data of many types, as well as climatic and meteorological data
- biological world: properties of the pathogen (ability to infect various species, potential for aerosol spread, survivability, etc.); locations, numbers and relationships of susceptible herds and flocks
- virtual world: everything connected to and available through the Internet, such as true and false information, disease reports
- c) Time this is the critical dimension. Time permits anticipation and response at home and abroad. If time is

gained, multiple alternate courses of action in space are possible. Generally, the more time there is the more options are available and the more likely it is that one or more of these options will be favourable. Conversely, the less time the fewer and less favourable the options.

Current transboundary disease surveillance strategies – and the responses disease outbreaks demand at home and abroad – ignore complexity, the virtual world, and, most importantly, the critical dimension of time. In most cases, our knowledge of the physical and biological worlds is also grossly deficient.

In almost all countries, suspicion of an outbreak of a transboundary disease begins when a farmer or veterinarian notices sick animals and calls a regional government official. The regional official travels to the site, examines the animals, and if a transboundary disease is still suspected takes samples for examination at a national reference laboratory. These samples are transported to the national reference laboratory where skilled technical staff attempt to identify the pathogen and thus to confirm the clinical disease diagnosis according to internationally accepted traditional methods. Non-traditional tests that test a region of the genetic material of the virus or bacterium that is a fingerprint (e.g. polymerase chain reaction [PCR]), may also be performed and have the advantages of being able to detect both live and dead pathogens at speed. But these tests are for the most part not yet recognised by the international community for formal diagnosis. If a transboundary disease is confirmed, or further more sophisticated tests are required, samples may be submitted to an international World Reference Laboratory. On confirmation, the country is required to notify the international community through the OIE. The entire process from first suspicion to formal notification typically takes many days and most countries are reluctant to disclose the existence of disease before formal confirmation.

The international and domestic surveillance system that is needed is not based on this historical precedent nor can it operate on the same languid timescale. What is needed is a system that achieves or approaches real-time understanding of the disease situation at all stages and in all places, i.e. a system that can be accessed over the Internet by diverse government agencies and stakeholders in the same country and in many countries through common software architecture and peer-to-peer networks so that each entity can keep its own data rather than have everything reside on one giant computer. Of course, this does not mean that all users have equal access to all data: tiered secured access is essential.

The current westward movement of AI H5N1 illustrates surveillance deficits at the international level. Spread has been through national and international poultry commerce and migratory birds. The latter's flyways are generally known, but this information by itself is of little use to government veterinarians seeking to implement active surveillance programmes (looking for disease in populations at risk) as opposed to passive surveillance (waiting for someone to discover and report dead birds). With limited financial resources, surveillance must be intelligently focused by knowledge of: the wild bird species infected at the point of origin in China; their migratory routes; specific sites along route where they congregate (and when); factors promoting congregation (to predict potential sites); and the presence of susceptible poultry. Public Health officials must also focus because infections are most likely in people in close contact with infected birds in high risk areas identified by veterinary authorities. Unfortunately, public health and animal health are two government departments that cooperate infrequently: wildlife disease surveillance often brings in a third department with poor communications. And critical knowledge of particular migratory birds is most likely found in private sector records of ornithologists or naturalists. The problem is in getting the right information to the right people in a timely manner so that optimal actions can be taken.

This example illustrates that the 2005-2006 AI outbreak is a complex system that involves at a minimum: global patterns of small farm agriculture (some 500 million enterprises) and international and national agribusiness; the patterns of human society in and between every country; the natural histories of hundreds of species of wild migratory birds; and, not least, the natural history of AI H5N1 itself. The physical and biological worlds associated with each of these have been hinted at above. For the first time, dwarfing that for FMD in 2001, we are witnessing the power of the Internet to begin to deliver information and shape public perception understanding on a global scale. An international disease surveillance system that can capture all these data and more must be developed. Furthermore, it must be capable of delivering insight as well as information to the end user in a timely manner related to the contemplated action.

Previously (1) the author has described the intellectual and technological basis for a national animal disease surveillance system that would be part of a government 'command, control and communication' system (CCC system). This type of system would be the means to track events in real time, for command and control at all levels, and for communication between all parties involved, including the public, media and local community and business leadership of all kinds. The CCC system would allow responsible authorities to lead a coordinated cooperative campaign with many other partners beginning immediately the problem is recognised and focusing all available local resources where they are most needed in the first hours and days. The goal is 'information to insight in real time'.

The CCC system must have an organisation structure that will allow state and national action and regulatory agencies to undertake at least the following five actions:

- a) observe, characterise and predict activities, both discrete events and patterns, across a minimum of the three venues (the physical, biological, and virtual) and the temporal world. Time is the critical dimension
- b) relate information from all venues promptly and synthesise the results into a form that can be disseminated to those who need to know in order that informed action may be taken
- c) catalogue historical events and also recognise emerging patterns of hazard, threat and opportunity in all the venues of human enterprise and natural phenomena to provide foresight and anticipation, the key ingredients of effective action
- d) communicate and present knowledge derived from this information in ways that provide force-multiplying support to the action agency personnel at the centre of the system
- e) provide timely, accurate, transparent, credible information to the public, media and local community leaders to promote understanding, allay unnecessary fears and prevent panic. Cable news channels must not be the sole source of current information for the public and local leadership.

In the example of FMD, the physical world would include wind, weather, and the location of personnel, disease detection equipment and other physical assets. The biological world would include demographic data on susceptible species and the aerosol characteristics of the exact type of FMD virus causing the problem. The virtual world means anything involving the Internet - including websites of advocacy groups with opinions relevant to the situation and the media. Public opinion in a crisis is not shaped by scientific results appearing after peer review in an academic publication. The Internet has unprecedented potential to drive public perception for good or bad and to shape action agency responses accordingly. The temporal world includes both chronological time and the relationships of events to each other in time. Here. examples would be the estimated times at which animals had been infected on the index farm and then became infectious for others, or the times when certain weather events occur or virus plumes are generated, and the relationship between these times and times of movements of people, animals and physical objects from farms in the data-defined quarantine zone.

To be a national seamless system for response to the full spectrum of disease threats, many historical and real-time data resources would also need to be available. Examples include: street maps; telephone numbers; topographic, ground cover and landscape maps; real-time satellite imagery; demographic data on population distribution; economic data by location; locations of specific businesses; water, sewer and other utility maps; medical resource maps; schools; law enforcement resources; locations of specialist auxiliary personnel and resources appropriate to a particular threat response, and so on. Each responsible agency would best identify the necessary resources in conjunction with all the anticipated partners at the national, state and local levels. Geographic information systems are now a vital component for optimum efficiency. All these would have to conform to set standards so that the whole is compatible.

Domestic preparedness for accidental and deliberate disease introduction

Animal agriculture in the USA (and Canada, Europe, South America, Australia and New Zealand) is perilously vulnerable to deliberate attack with foreign livestock viruses. Traditional government responses to such an event - sweeping quarantines, mass slaughter and burning or burial of millions of carcasses under the ceaseless eye of television - together with staggering financial losses triggered by international trade embargoes are exactly what terrorists want to see and what makes these viruses potential BW in the first place (1). The US policy to counter agroterrorism is fatally flawed because it mistakenly conflates the threats of inadvertent and purposeful disease introduction. Moreover, this policy was developed without understanding that it is only the ways in which the country has chosen to respond to foreign diseases in the past that allow terrorists to threaten it with them in the future.

As American and international agribusiness has industrialised, animal health officials have stubbornly clung to 18th Century ideas of epidemic disease control, despite abundant recent evidence from Taipei China, the Netherlands and Great Britain that in the context of modern agribusiness such actions guarantee catastrophe. If we try to counter deliberate assaults the same way, after a successful attack it will be national governments, not a terrorist gang, which is killing, burning, filling mass graves and wreaking economic havoc nationwide. In 2006 these are the wrong responses to either inadvertent or deliberate disease introduction and the consequences of this mistake cannot be limited to farmers: there will be lasting damage to the rural economy and public confidence in government and enormous costs for taxpayers. Should the foreign disease infect humans as well as livestock - as is now the potential with AI H5N1 - our families will also be at risk. All of which will greatly embolden and encourage terrorists.

Terrorist attacks on a nation's agriculture are not about imperilling food supplies: they are about terror, money, mass slaughter and funeral pyres all day every day on the international Cable News Network (CNN). National policy for inadvertent and deliberate foreign animal disease introductions should be simple: it should aim to minimise direct and indirect economic impacts and to not implement a policy of mass slaughter. Fortunately, most of the tools and technologies to permit such a policy already exist. There are now rapid, on-farm tests for these diseases; effective vaccination strategies; Internet-based command, control, and communication systems; and means to track animal products from farm to table in real time, even internationally. These allow for a more effective response than was possible 300 years ago and permit a new national policy. If countries in the developed world choose this way forward, there will be little point in deliberate attacks because the outcomes terrorists want to see will not be possible and inadvertent introductions will be eliminated with scarcely a footprint. But changing national policy will require input from a much broader group of policymakers than in the past: given the nature and magnitude of what is at stake this is not just a matter for agriculture any more.

The state of current preparedness is inadequate, everywhere. For at least 20 years it has been obvious that the modern agricultural industries of the developed world cannot use 18th Century methods to control naturally or intentionally occurring outbreaks like FMD in 21st Century agribusiness without catastrophic damage and enormous economic costs. To try to do so is a grave mistake and there are much better alternatives.

Government policymakers need to understand that:

- a) control of inadvertent or deliberate FMD or other transboundary livestock diseases is not an animal health policy issue that can be left to agricultural authorities
- b) traditional inadvertent outbreak controls are based on financial factors, not animal health the 'best' response has been the one that triggered the lowest costs for agriculture, not the whole economy
- c) terrorist attacks on animal agriculture are not aimed at denying the public food supplies, killing farm animals or making them sick; they are intended to produce terror, staggering financial losses, mass slaughter and funeral pyres theatre that can be shown all day on television at home and abroad to demonstrate the capability of groups to strike at the heart of a country and to attract recruits and support
- d) the damage from FMD, however introduced, comes from our response not the infection itself
- e) the present response is conditioned by tradition

- f) the current method of responding is what makes these transboundary livestock diseases terrorist weapons in the first place
- g) most of the tools and technologies to allow new policy already exist; governments have just chosen not to use them.

With a policy that minimises direct and indirect economic impacts and does not require mass slaughter there is no theatre, nothing to show on television, no triggering of sweeping, costly trade embargoes, and little point in a deliberate attack. Governments can implement this new policy tomorrow and work with the OIE and World Trade Organization to modernise international regulations on animal health so that all countries that wish can follow the same path.

Fortunately, over the past decade the USA has developed the core technologies to implement this new policy and others will flow once the incentives are there. The principles of their operation and potential applications are described elsewhere (1). The key innovations were:

- a) rapid, on-farm real-time PCR diagnostic tests that can be read by experts at a distance in real time over the Internet
- b) a real-time, Internet-based CCC system to coordinate federal, state and local responses
- c) a differential test that discriminates FMD vaccinated animals from those that have recovered from disease yet might still be infectious for others
- d) tracking and identification systems to follow animals and products from farm to table through the entire production and processing chain, and even internationally.

Logically, similar systems can be developed for other transboundary diseases. Unfortunately, the USA, and other countries at risk, have chosen not to use these powerful tools, largely because there is enormous confusion at the policy level stemming from the proximity of the 2001 FMD outbreak in Great Britain – which caused even the most stubborn mass slaughter proponents to have second thoughts – and the terrorist attacks of September and October 2001, which are the events that first brought deliberate attack and BW into sharp focus for most people. As a result, there is conflicted thinking about: inadvertent introduction and catastrophes abroad, biological warfare, and agroterrorism.

To understand how the new policy would work, we need clarity about:

- a) the nature of the threat
- b) the nature of national vulnerability

282

- c) the factors that make new policy a necessity
- d) future technologies to prevent disease or cut financial losses
- e) necessary changes in the relationship between government and industry that will enhance defences and minimise the impacts of disease.

The threat

Biological warfare has been planned or employed by many nation states over history as an adjunct to conventional weaponry. But it is not a current threat to any nation's agriculture. In World War II, there were plans (and even limited actions) to use BW that caused disease and death in animals and plants on a large scale as an act of war intended to cause hunger and deny food to the opponent's civilian population and armed forces. Most recently, the former Soviet Union clearly had the weapons, the delivery systems and the production capacity to threaten US food supplies in time of war. But such a threat does not exist today and it is highly improbable that a terrorist group has the capability and capacity (or intent) to provoke hunger in the USA by waging biological warfare against animal and plant industries. Specifically, one can discount the idea of kilograms of virus or fungus being dispersed by crop sprayer over vast populations of animals or acres of crops.

Thanks to current policy, terrorists, however, need only have capability – not capacity – to successfully attack agriculture in the USA and other developed countries. Terrorists want to see a dramatic public result that attracts media attention. Such results can only be triggered by attack on a big target – one or more of the dairy, beef, swine or poultry industries – with a transboundary livestock disease pathogen which leads to mass slaughter and costly international trade embargoes. Furthermore, to produce an epidemic, the pathogen must be easily spread by aerosol, direct contact or a flying insect vector beyond the initial site of attack. Only a handful of pathogens, all viruses, meet these criteria, as follows:

- FMD in cattle and swine
- rinderpest in cattle
- classical swine fever (CSF) and African swine fever in pigs
- AI and Newcastle disease viruses in poultry
- Rift Valley fever (RVF) virus.

The latter is a mosquito-borne virus of humans, cattle, sheep and goats; its significance as a terrorist weapon, like that of AI H5N1, depends less on its impact on agricultural economics and mostly on the ability of infected livestock and insects to serve as reservoirs for human infections.

The list of realistic terrorist livestock weapons threats is necessarily much smaller than the list of foreign viruses, bacteria, parasites and insects included on the OIE list of notifiable diseases that might be inadvertently introduced into a disease-free country like the USA in the course of normal international travel and trade. Such introductions would of course have consequences and would stimulate a government control response. But their nature is such that this response will be insignificant compared to FMD and the other six viruses listed above. The US Department of Homeland Security currently lists FMD, RVF, AI and Brucella as priority threats to agriculture in the USA. Brucella species cause disease in cattle, swine and sheep and also infect humans. Terrorists can threaten humans with Brucella (by aerosol release) but they could not threaten agriculture because such infections in livestock do not trigger mass slaughter or international trade embargoes. They are economically insignificant. Nor would terrorist infection of livestock with Brucella threaten human health - for decades the public has been protected by pasteurisation of milk and cheese. This was clearly shown in 1999 when Brucella melitensis was found in goats and cattle in Texas, probably after introduction from Mexico. The focus was eliminated without an economic ripple.

An advanced BW is one whose biological properties have been modified by genetic engineering or other means to defeat countermeasures. As an example, Soviet scientists added a novel toxin gene from another microorganism to *Bacillus anthracis* in an attempt to defeat the US military vaccine. There are thus two challenges in detecting BW:

- a) to detect the known pathogen
- b) to detect an advanced pathogen that has been modified genetically (and to understand the nature of the modification so as to develop countermeasures).

Governments thus seek to defend their countries against known disease agents and to anticipate and defend against technological surprise through advanced BW with unexpected properties (1, 6).

Eliminating or even totally eradicating FMD or any other transboundary livestock disease will not completely remove the threat of terrorism or future biological warfare employing this virus. Eliminating FMD would certainly make terrorist access to virus more difficult in the future; the purpose of the Biological Threat Reduction Program (BTRP) (see next section) is to make access very difficult under current conditions. But the world's most dangerous BW – once manufactured in large quantities by the former Soviet Union – is smallpox virus, the cause of a human disease eradicated globally almost 30 years ago. The end of smallpox as a public health problem also spelled the end of routine vaccination of the world's population and closure of vaccine production facilities. Today, the entire world

population is as vulnerable to smallpox as the peoples of the New World in 1492. Even if all world sources of FMD virus were to be destroyed – an improbable and immeasurable event – new virus could be made synthetically (FMD virus is a relative of polio virus, which has already been made in the test tube from scratch) and engineered to evade all known vaccines. We will thus need to maintain our defences against eradicated diseases to counter any future uses.

The nature of national vulnerability in the USA

The largest agricultural market in the world is the USA and this depends upon very large populations of domestic livestock and poultry. These flocks and herds are individually very large – just 2% of feedlots produce over 75% of the cattle – and for economic reasons the different industries have become clustered in a handful of states: 75% of swine are in the mid-West, 80% of broiler chickens are in the Southeast and over 80% of feedlot cattle are in the mid-West and Southwest states. As a result, very large populations of animals are at risk in small areas. These animals and birds have little or no innate resistance to foreign pathogens and, by policy, are not vaccinated against these diseases, which do not occur in the USA under normal circumstances. Similar situations pertain in other countries at risk.

The animal and poultry production, slaughter, processing and distribution system in the USA is highly integrated and characterised by rapid movement of vast amounts of product over broad geographies and through many hands from farm to fork. This system, which is highly efficient economically, could only develop over many decades because the USA was free of major animal diseases that might have hindered unrestricted inter-state trade. The system now embraces Canada and, to a lesser extent, Mexico and is becoming increasingly global. Of course, producers always realised that the possibility of inadvertent introduction of a foreign disease posed a constant threat but that seemed remote. As a result, US agribusiness never factored the consequences of introduction of a highly infectious, highly contagious disease into the production and processing system. And government did not do this either. Today, the USA is so vulnerable to inadvertent or deliberate introduction because it chose to build the system that way.

Factors that make new policy a necessity

The USA has been extraordinarily fortunate not to have experienced a major foreign disease epidemic in livestock or poultry over the past 20 years. Among the geopolitical changes that have greatly increased the potential for inadvertent disease introduction are: the fall of Communism; increased volume and globalisation of trade; expansion of the European Union; free trade agreements;

containerised shipping; reduction of government investment in disease control, regulation and inspection of agricultural products; and liberalised international travel with direct flights to the USA from formerly distant parts of the world. These factors should have stimulated new policies to reduce vulnerability, but they did not.

Future technologies to prevent disease or cut financial losses

Almost to the end of the 20th Century, the only way American business could be threatened by a foreign virus was by accidental importation of FMD, rinderpest or some other threat. In 2006, however, American business is far more likely to be damaged by a computer virus delivered over the Internet from some foreign shore. The costs of such attacks can be considerable and even exceed those often quoted for FMD. Yet government has adopted quite a different approach to the business costs of foreign transboundary computer viruses as compared to animal and plant transboundary viruses. Government sponsors and encourages research on computer defences and supports law enforcement efforts to catch those responsible. But business is entirely responsible for the costs of staff, software and training to prevent or mitigate attack and for back-up systems to maintain key functions. If a company or individual chooses not to use these protections, they are free to go out of business when crippled by a computer virus attack.

In the 18th Century, farmers whose cattle had rinderpest did not receive compensation: those who did not report the disease were hung, drawn and quartered. But a century later the promise of compensation did increase reporting and helped end epidemics. In 2006 government compensation is one of the factors that promote industry complacency about inadvertent and deliberate threats. If all sectors of the industry had to insure against these losses instead of relying on government there would be immediate changes: private insurance companies would never accept the risky practices that have become engrained.

Government and agribusiness have built a tremendously vulnerable system that could be devastated by inadvertent or deliberate pathogen introduction. Yet some business sectors have opposed or blocked some of the very tools that are essential to mitigate losses if disease should strike: animal identification; country of origin labelling; bioterrorism prevention and preparedness steps; and identification and tracking of product. No licences or tests are required to farm animals, there are no rules or standards for farm or premise biosecurity and few employees are trained to prevent or detect disease. High-risk practices are common and the industry structure promotes them. For example, feeding garbage to swine is a very high risk practice by which FMD and other foreign

viruses can get a foothold to start an epidemic: the practice is only profitable if the risks are passed on to society in general. If the garbage is properly cooked the risks are minimal, but it is everyone's cooking that must be perfect, not just an individual's. It is not clear just why it is a societal responsibility to compensate the garbage feeder whose pigs get FMD: this is not different from a computer virus. And it seems unconscionable to compensate the garbage feeder but not the slaughterhouse worker and hotel owner who lose their jobs as a consequence of his actions. The answer is not to extend the scope of government compensation but to curtail it. If all farmers had to acquire insurance against the costs of FMD and other transboundary diseases, those that engaged in high risk practices would probably not be able to purchase insurance and would go out of business. This is not entirely a bad thing, even for other farmers: those that remained would adopt far more stringent practices for all inputs to their agricultural enterprise, as is commonplace for other industrial sectors.

Changing government-industry relations

But this is very definitely not to paint agribusiness as an adversary. The industry is the only player that can reduce national vulnerability through peer example and pressure. The industry is painfully vulnerable. This will not be solved by government rules and regulations. Industry itself has to take the initiative and government can best assist by using its penalties and inducements to encourage movement in the right direction. Of course there are already agricultural businesses with very high standards of biosecurity. These are the ones able to exert the necessary degree of process control throughout their operations. They are the benchmarks for others.

A new benchmark for veterinary surveillance and detection

The US Defense Department's Defense Threat Reduction Agency is engaged in a Biological Threat Reduction Program (BTRP) in some countries of the former Soviet Union: currently these are the Ukraine, Georgia, Azerbaijan, Kazakhstan and Uzbekistan, which together cover a broad swath of territory from the Polish border to the People's Republic of China. The overall purpose of the programme is to prevent proliferation of BW technology, pathogens and expertise at the source. This is accomplished through four interlocking activities designed to:

- a) prevent the sale, theft, diversion or accidental release of BW materials, technology or expertise
- b) consolidate especially dangerous pathogens (EDPs) into safe, secure central reference laboratories

- c) improve national capabilities to detect and respond to EDP disease outbreaks
- d) integrate government scientists into the international scientific community
- e) eliminate any residual BW infrastructure and technologies.

Threat Agent Detection and Response System

The Threat Agent Detection and Response (TADR) system is the BTRP component charged with enhancing reporting, detection and response capability for human and veterinary EDPs, including wildlife reservoirs and vectors. The term 'EDP' has a specific legal definition in each country and the BTRP priority agents include some pathogens that are not classified as EDPs in all countries, yet are of mutual interest.

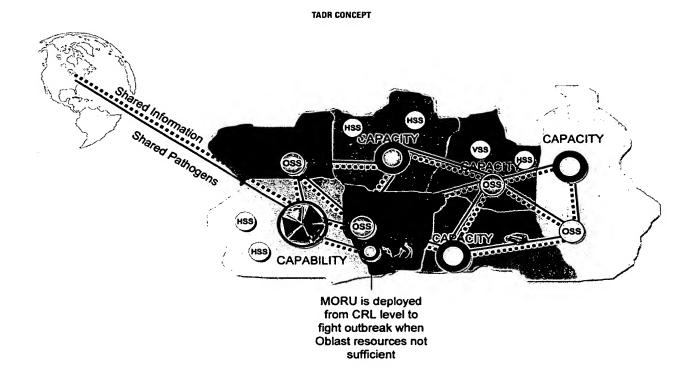
The TADR system is not intended to be yet another surveillance system but to be integrated into existing country surveillance and diagnostic systems operated by agencies of the Ministry of Health, the Ministry of Defence and the Ministry of Agriculture, so the following description of the general system architecture (see also Fig. 3) is modified according to individual country circumstances.

National level

At the national level, central reference virology and bacteriology laboratory capabilities are enhanced to provide biological safety level 2 and 3 laboratory and animal research space that complies with international standards for employee and environmental safety and for biological security. (There is a distinction between 'biological safety', which is intended to protect laboratory personnel and the environment from EDPs inside the laboratory and 'biological security', which is designed to prevent theft or unauthorised access to EDPs.) Laboratories are equipped to perform modern molecular tests, such as enzyme-linked immunosorbent assay (ELISA) and realtime PCR, as well as culture and traditional tests. Specialised transport is provided to allow rapid epidemiological investigation of suspicious cases and collection, safe packaging and secure transport of samples. The central reference laboratory serves four functions:

- a diagnostic laboratory for the city or region in which it is situated
- a national reference diagnostic capability
- a secure EDP repository (with electronic control of the pathogen inventory)
- the national locus for research with EDPs.

285



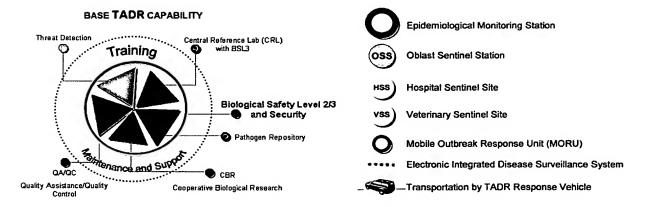


Fig. 3
Elements of the Defense Threat Reduction Agency's threat agent detection and response (TADR) system

Also managed at the national level are two rapid response teams, one for human health and one for veterinary health, each with appropriate cross-training to work together on zoonotic diseases. These are deployed by the Minister of Health or the Minister of Agriculture when resources at the regional level are not sufficient to contain the outbreak. The rapid response teams have portable PCR capability to provide additional disease detection capacity at the site of the outbreak and mobile access when deployed to an electronic infectious disease surveillance system (EIDSS) see below.

Regional level

At the regional level there are existing public health and veterinary epidemiological and diagnostic laboratories in every region (known as an oblast, which is larger than a county or canton but smaller than a state or province). These are the backbone of the existing system. All these laboratories are being upgraded by provision of an EIDSS; dedicated vehicles for case investigation, sample collection and transport; and biological safety equipment for collection, processing and packaging of samples. In addition to this

some laboratories are also being supplied with modern molecular tests, including ELISA and PCR. Laboratory detection activities will be at biological safety level 2. The EDPs will not be stored at these regional laboratories: after the detection test they will be destroyed or sent to the central reference laboratory for further analysis and characterisation as warranted.

Often it is not economically justifiable, or even physically possible, to renovate existing buildings to meet international biological safety and security standards, especially in regions of high seismic activity. Therefore, a new pre-engineered facility has become the standard model at the oblast level to provide the full range of surveillance, diagnostic and reporting capabilities. The numbers of oblast laboratories differ between countries, based in each country on geography, the distribution of susceptible human and livestock populations and knowledge of past and active foci of disease, such as tick reservoirs or porous borders across which small ruminants move without interruption. In Georgia there will be a total of three veterinary laboratories and in Uzbekistan six. For these regional veterinary laboratories, dedicated transport to investigate outbreaks on farms and to collect and transport samples under conditions optimal for subsequent laboratory diagnosis is critical.

District level

At the district level (known as a rayon) public health and veterinary officials will be trained in disease recognition and reporting mechanisms. This system is based on a three-tier case definition approach starting with a 'suspicious case' at the farm, hospital or rayon level, going to 'probable case' after a positive pathogen detection testing procedure at the oblast laboratory and ending as a 'confirmed case' after regulatory-approved tests at either the oblast or central reference levels. Certain infectious disease hospitals and slaughter plants that might be expected to encounter a significant number of cases will also receive biological safety equipment and training to ensure samples are collected and stored properly.

EIDSS: Electronic Infectious Disease Surveillance System

The EIDSS provides the means to report suspicious disease outbreaks in real time and to track the progress of case investigations, epidemiological investigations in the area and the results of sample testing. The EIDSS contains a GIS and will locate disease outbreaks by use of a geographical positioning device. This is vital when street addresses, premise identifiers, and unique animal and personal identifiers are not available. Historical records of disease distribution will also be incorporated. The system has the ability to track multiple samples from the same patient taken at different times and places. There are built-in links between human and veterinary health for cases of zoonotic

disease. Although initially confined to the EDP list of diseases, the EIDSS is intended to encompass all public and animal disease surveillance information in the future. The EIDSS data is entered in the language of the country but can be searched in many languages. Combined with the rapid results obtained from real-time PCR detection, the EIDSS can report positive laboratory detections in close to real time, at most in a few hours depending on distance. The Rapid Response teams will be able to detect and report from the site of the outbreak should that be needed.

International standards, quality control, training programmes and regulatory changes

The TADR system uses the same equipment, test protocols and test reagents in all countries and the results are intended to be fully compatible with standards of international organisations like the World Health Organization (WHO) and of the US Centers for Disease Control and Prevention. There is a quality control and quality assurance programme and the laboratories will meet international performance standards. There is an extensive training programme in every aspect of this very new system: operation and maintenance of laboratory infrastructure; operation and maintenance of laboratory biological safety and analytical equipment; epidemiology and disease surveillance techniques; laboratory assays and their quality assurance. Extensive regulatory changes have to be made to existing country laws and regulations to accommodate unfamiliar concepts, equipment and procedures. This is an enormous task that could never be completed without earnest support from the countries themselves. Critical to success in matters that fall under many departments of government is an agreement at the Presidential or Cabinet level that the National Security Council and the Ministries of Health, Defence, Agriculture, Justice, Finance, Foreign Affairs and Customs and Excise will work together to identify and overcome barriers.

Technology is outpacing regulatory capability

The TADR system provides the architectural backbone for a more extensive nationwide detection and reporting system that will cover common diseases as well as EDPs and is a model that can be extended to other countries by other funding sources. With the TADR architecture in mind, the impacts of future technology can be anticipated.

The TADR system is using real-time PCR tests that identify pathogens one by one in a highly sensitive and specific manner. These tests are the state of the art for answering the question: is this a case of FMD or not? It would require three separate real-time PCR test procedures, which could proceed simultaneously in the same machine, to answer

the question: are FMD virus, CSF virus and African swine fever virus present in this sample? Many tests would be required to determine the cause of a fever of unknown origin, although specific causes could be ruled out one by one by single tests. The reason for this is that there are inherent limitations on the number of fluorescent dyes that can be used and discriminated in a PCR test procedure when testing for multiple pathogens at the same time (a multiplex test). The next generation is one of multiplex tests that can detect all transboundary pathogens in a single procedure. PCR technology using various combinations of 64 distinct molecular mass tags instead of dyes can identify many pathogens simultaneously. With this approach, 22 different viral, bacterial and Mycoplasma respiratory pathogens (2) and ten different causes of viral haemorrhagic fever (10) can be simultaneously and rapidly discriminated in human clinical samples. Mass tag PCR costs about the same as real-time PCR except for the onetime cost of the mass spectrometer, but it is a logical next step up diagnostically from single PCR tests: the technology also builds on experience with PCR and quality assured laboratory practices. The latest generation of microarray tests incorporates 30,000 viral, bacterial and parasite genetic sequences representing all vertebrate infectious agents on a single chip (W.I. Lipkin, personal communication and unpublished data, 2006). The technology for microarray chips that can detect all livestock (not just transboundary pathogens) infectious agents simultaneously is already upon us though their current production cost makes them too expensive for veterinary use at the moment.

The trend in technology is crystal clear. Technology has already allowed tests that could once only be conducted in sophisticated national reference laboratories to be conducted in less elaborate regional laboratories at lower levels of biological containment or on the farm. It has also allowed tests that even national reference laboratories could not do to become commonplace at the regional level. With time and money, and a firm basis of experience with current technologies, the TADR model will become increasingly sophisticated at the regional and lower levels, as well as centrally. This has significant implications for how transboundary disease diagnosis is regulated and approved at the national and OIE levels and for the future roles of the World Reference Laboratories, which are more likely to be handling viral and host genomic information transmitted electronically from the countries themselves rather than actual samples of virus from which information has historically gone in the opposite direction.

The research that defined real-time PCR tests for FMD, CSF and other transboundary diseases, was disclosed and demonstrated to veterinary regulatory agencies in the USA and Great Britain and to members of the US Animal Health

Association in 2001; the scientific paper was published in 2002 (3). In 2006, a joint effort by British and US FMD diagnostic scientists essentially confirmed what was known in 2001 (7). But the test has still not been recognised by the OIE for international use for the diagnosis of FMD, even though the 2006 study (7) rediscovered that it would detect the presence of dead virus that could not be grown in cell culture and was, therefore, the new state of the art, as it had been since 2001. 'Validation' studies on the other tests are still in progress. In the meantime, there have been three highly significant technology advances: mass tag, FilmArray and the multi-pathogen chip. Our regulatory approval processes are completely broken when they cannot even keep up with generations of technology, far less specific applications. Transboundary disease diagnosis will never go back to being the province of a small club in select laboratories. We need to get these new generations of tests validated and out where they can be used within one year or less from discovery. The matter of pathogen detection has been trivial for some time and the tough question has become how to best use the new tests and the information they generate.

There are repeated calls for cheap, rapid pen-side tests that can detect FMD and other pathogens. This was identified as a critical need during the 2001 British FMD outbreak and in a recent European report (5). Such tests have existed for some years. The FMD real-time PCR test (and others for CSF, etc.) was always intended to be the trigger for regulatory action and response when used to detect and report infection, in close to real time, from the index farm over the Internet. But these tests have far greater potential. The challenge, immediately FMD is detected, is to discover where it is already present on other farms in the immediate area (tracebacks) and distantly. In the case of dairy farms, this could be done by positioning PCR machines at milk processing plants to test every truckload of milk delivered: detection in milk would immediately identify the farm(s) infected without regulatory officials stepping on the premises. More importantly, this also allows milk to continue to flow, thus turning a serious environmental disposal problem on the farm into a continuous active surveillance tool. The differential test that discriminates animals vaccinated against FMD from those that were previously infected should also not be limited to rare use in developed countries after vaccination programmes. In countries that do vaccinate, there is no easy way, short of having government employees administer the vaccine, to be sure that farmers are actually giving it to their stock (the expense of vaccination is in catching and injecting the animals, not in the vaccine purchase cost). The differential test might be more usefully used in producer managed regional FMD eradication programmes in which animals from herds in the region are tested as they passed through the slaughter plant to verify that producers had vaccinated their stock. Failure to do so would result in denial of

slaughter facilities in the region and intense peer pressure to vaccinate.

Recruiting others to the cause

The time is right to broaden the base of public support for transboundary disease elimination beyond the traditional animal health community. Those who are interested in public health, alleviating poverty, the environment, controlling the trade in exotic and endangered species, preservation of wildlife habitats, and animal welfare all have a stake.

Public health in Africa

Elimination of transboundary livestock diseases must advance hand in hand with the major investments now being committed to global public health programmes. The World Bank, the Bill and Melinda Gates Foundation, the US government and others have committed billions of dollars to develop and deliver vaccines and therapies for infectious diseases devastating the peoples of Africa and other parts of the developing world. Former US President Bill Clinton also emphasised the impact on African health and productivity of such common infections as malaria, sleeping sickness, human immunodeficiency virus, and tuberculosis and proposed that these be regarded as a national security issue for the USA. President Bush announced plans to double US foreign aid to improve global human health and has committed new funds to control AIDS internationally. The United Nations has launched a Global AIDS Fund to provide low cost medications for this disease. There is renewed interest from the international community in bringing new technologies to bear on solving these problems: there should be optimism about the chances of long-term success. But success in improving human health will not achieve its full potential unless a parallel effort is made to improve the health of domestic livestock in Africa and the developing world. When millions of new African and Asian lives have been saved, it is not well appreciated that their futures will still be very bleak without livestock and the many benefits they provide.

An international non-governmental initiative is required to envision, advocate, organise, catalyse and lead the effort to bring the same modern technologies that will solve the human health problems to bear on the major infectious livestock diseases of Africa and the developing world. Such a programme is likely to have immediate and significant successes that will reduce hunger and poverty and improve the economy at the micro- and macro-levels in many countries. At the same time, the threat of accidental or deliberate introduction of dangerous animal diseases into

countries such as the USA, Europe, Australia and New Zealand will be greatly reduced or eliminated.

The global importance of livestock

Livestock are vital and irreplaceable in human societies and not just for food. They play critical yet oftenoverlooked roles in less-developed countries, where they have a very special place in the lives of the rural poor, particularly the poorest of all. In South America, Africa, the Middle East and Asia, livestock are relied upon as (4):

- a key source of human food and food security
- the sole form of nonhuman transportation and draft farm power to pull carts and ploughs
- the major asset bank and insurance source where no other financial markets exist
- an important source of cash income, especially for the very poor
- one of the few assets available to the poor, especially poor women and widows
- a means to provide manure and draft power to preserve sustainable soil fertility
- a way for the poor to exploit common property resources to earn income
- a source of diversified farm income
- the origin of inputs for other value-added industries, e.g. leather, shoes, clothing etc.

When diseases destroy herds and flocks, the consequences are far more profound than just loss of food — it is a simultaneous loss of one's job, tractor, car and life savings. People in North America, Europe and other regions where these diseases do not occur — where there are no longer pastoral societies dependent upon herds and flocks of cattle, camels, sheep and goats — have little concept of their impact elsewhere. Elimination of these diseases will gain support from those committed to removing poverty through its root causes.

Healthy livestock in a sustainable environment

Eliminating transboundary livestock diseases in developing countries will not result in larger flocks and herds, and greater environmental degradation — desertification, overgrazing and soil erosion. Healthy livestock herds and flocks can be managed for a sustainable environment. The means to achieve these goals are known and much attention has been paid to management systems that promote a sustainable environment. Critical issues of sustainable agriculture and livestock production in Africa have been

addressed by Delgado and others (4). In a comprehensive review of the subject, they gave particular attention to environmental, food safety and human health concerns. These are complex topics, but to summarise: there is every reason to expect that a new initiative in transboundary disease elimination can be part of a broader effort already under way with much international support to create a sustainable livestock industry that advances the poor and yet protects the environment. Rapidly increasing livestock numbers can cause serious environmental damage but can also be harmonious with, or even beneficial to, the environment when appropriate types and levels of production are in place. The International Trypanotolerance Center in the Gambia illustrated the possibilities by demonstrating that large numbers of Trypanosoma-tolerant cattle could be sustainably managed at the village level with native food resources.

Trade in exotic animals and endangered species

Tens of millions of wild animals and birds are shipped around the world each year, often illegally to evade international regulations that protect endangered species. These animals are used for food and medicines in Asian markets, in illegal and legal cockfights in the southern US states from California to the Gulf of Mexico, in the pet trade, and for other purposes. The range of species used for human food is far wider in Asia than in the West and this provides an increased opportunity for emerging pathogens to pass from these wild species to humans, especially under conditions where many species are held together in unsanitary high-density conditions in live animal markets where the animals may also be killed and prepared for human consumption. These wild animals may also carry transboundary diseases of livestock. This is an enormously difficult trade to regulate or to prohibit. The danger is that regulation will drive the trade underground where it may be more dangerous even though fewer animals may be involved. Eliminating transboundary disease will have no impact on the scale or ethics of the wild animal trade except to make it safer from the point of view of humans and domestic species that are also exposed. Strengthening border controls and establishing effective shipment inventory, tracking and origin records will deter smuggling.

Wildlife conservation

In Africa, especially Central Africa, the trade in 'bush meat' (hunted wild animals), especially endangered primates, is on a staggering scale. Bush meat is also smuggled abroad. The amounts are necessarily not known exactly but are believed to be very considerable. This meat poses very significant risks of disease transmission to humans (Ebola virus particularly) and to livestock. Eliminating transboundary livestock diseases will reduce the need for people to rely on bush meat when other meat is available.

The prospects for success are good: if we give them the tools they can finish the job

Developing countries do not have the research and technology base to invent by themselves the vaccines, diagnostic tests and other technologies necessary to control dangerous livestock diseases – but when these are made available countries can employ them successfully. If developed countries give them the tools they can finish the job. The evidence for this is the remarkable progress in global eradication of rinderpest over the past 20 years, organised by the FAO.

Rinderpest was once the world's most dangerous animal disease. But through international efforts, rinderpest has now been almost completely eradicated worldwide, except for small foci of infection in East Africa. Over the past few years eradication has proceeded in some very troubled parts of the world despite wars and political problems.

The other major infectious diseases may be more difficult to control technically because the microorganisms that cause them have evolved abilities to disable the immune and inflammatory defences of the animals they infect. While developed nations have created many new technologies intended for their own protection, they have not effectively transferred these technologies to the countries where the diseases are prevalent and where an ounce of prevention can help to prevent devastating epidemics both there and elsewhere. The next steps must be to ensure that the necessary vaccines, diagnostic tools and other technologies are developed into real products and made available to the national and international agencies that can use them. Much of what is needed is already available. The problem is the governmental and institutional barriers - many self-imposed - that need to be overcome to get these into the hands of those in the field. The missing link is a non-governmental organisation (NGO) that can ensure by advocacy and direct action that research and development deficits are filled, that regulatory hurdles are overcome, that new policies for deployment are developed and that efficacy is clearly shown by well-designed demonstration projects. Such an organisation should not be actively engaged in disease control and eradication programmes per se. There are established governmental organisations and NGOs that can accomplish this task if they have the necessary tools and technologies and a valid strategy.

The new organisation would tackle the world's most dangerous livestock diseases – diseases that are so significant economically for agricultural industries in developed countries that their study and control have

290

traditionally been under strict government control. Some might question the need for private enterprise in an endeavour that seems entirely in the realm of national governmental responsibility. But two of the main reasons the current global disease situation has become so dire are that study and control of these diseases have always been a government monopoly and that international cooperative initiatives have predominantly been government-to-government relationships. Governments have focused on their self-interests and international organisations have had too many other unrelated agendas for effective solutions. It is exactly because private initiatives have been so few and governmental monopoly so universal that the moment is ripe for an alternative agenda.

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Technologie, action publique et contrôle des maladies animales transfrontalières au cours des prochaines années

R.G. Breeze

Résumé

Il n'existe pas d'obstacles technologiques à l'élimination des principales maladies animales transfrontalières. L'« élimination » signifie que les maladies ne constituent plus une menace ni pour le bétail dans les pays développés, ni pour la subsistance de centaines de millions de petits éleveurs ailleurs. Le problème ne réside pas dans l'insuffisance des capacités technologiques, mais dans l'échec des politiques publiques. La politique des pays développés doit viser à lutter activement contre l'introduction accidentelle et intentionnelle d'agents pathogènes, à protéger les animaux d'élevage contre les prochaines armes biologiques de pointe, à réduire autant que possible et par tous les moyens l'impact économique d'une introduction éventuelle, à renoncer à recourir à l'abattage massif en tant qu'outil de lutte, à s'engager en faveur de l'élimination des maladies dans le cadre d'un programme mondial axé sur l'économie, la société et l'environnement, enfin, à faire les bons investissements nationaux et collectifs. Le temps est venu de changer de politiques puisque l'élimination des maladies animales transfrontalières concerne désormais de puissants ministères outre ceux de l'agriculture qui s'inquiètent des menaces sanitaires provenant de nombreuses sources. Le changement peut être appuyé par la population et par de nombreuses organisations qui partagent des intérêts communs. Il faut une nouvelle politique pour éliminer l'idée selon laquelle l'État est le seul responsable de l'éradication des maladies, de la réaction devant les introductions d'agents pathogènes et de l'indemnisation des éleveurs pour les pertes subies pendant l'éradication. L'efficacité des programmes de contrôle aux frontières et de préparation nationale aux situations d'urgence dépend de la collaboration des autorités et des entreprises dans une action dont les coûts incombent aux personnes responsables sous la forme de « redevances d'utilisation ». L'indemnisation pour les animaux abattus pendant la lutte contre une maladie devrait être couverte par une assurance privée. Le gouvernement et les entreprises devraient partager les coûts des systèmes de surveillance, de diagnostic et d'intervention. La surveillance doit arriver à saisir, en temps réel ou

presque, la situation sanitaire à toutes les étapes de la maladie et dans tous les lieux où elle sévit; elle doit être accessible par internet aux divers organismes publics et parties prenantes dans le pays et à l'étranger. Les réactions traditionnelles doivent être abandonnées parce qu'elles encouragent le terrorisme. Il faut moderniser les processus réglementaires d'autorisation car ils ne peuvent plus suivre les progrès de la technologie.

Mots-clés

Agent pathogène particulièrement dangereux — Amplification en chaîne par polymérase — Assurance couvrant les pertes dues à l'apparition de foyers — Détection des agents qui constituent une menace et mesures prises contre ceux-ci — Maladie transfrontalière — Nouvelle technologie — Politique d'abattage — Responsabilité — Surveillance — Système électronique de déclaration des maladies — Système de maîtrise, de contrôle et de communication — Vaccination.

Tecnología, políticas públicas y control de las enfermedades transfronterizas del ganado en unos pocos decenios

R.G. Breeze

Resumen

No hay factores tecnológicos que impidan eliminar las principales enfermedades transfronterizas del ganado. "Eliminar" significa acabar con la amenaza que las enfermedades suponen para el ganado en los países desarrollados y para el sustento de cientos de millones de pequeños ganaderos en el resto del mundo. El problema no reside en la falta de medios técnicos sino en el fracaso de las políticas públicas. Un país desarrollado debe aplicar políticas que sirvan para: combatir activamente la introducción deliberada o accidental de patógenos; proteger al ganado de las armas biológicas avanzadas que puedan surgir en el futuro; reducir al mínimo las consecuencias económicas de la penetración de un patógeno por cualquier medio; renunciar al sacrificio masivo como método de lucha; participar en la liquidación de enfermedades como parte de un designio económico, social y ambiental de carácter planetario; y realizar las adecuadas inversiones dentro del país y en régimen de cooperación. Ahora es el momento de imprimir un nuevo rumbo a las políticas, toda vez que el objetivo de eliminar las enfermedades transfronterizas del ganado federa a una serie de ministerios poderosos que, junto a los de agricultura, están preocupados por amenazas sanitarias de muchos orígenes distintos. Esta nueva orientación puede gozar del apoyo del gran público y de muchas organizaciones que tienen intereses en común. Se necesita una nueva política para cambiar la arraigada mentalidad según la cual el gobierno es responsable único de erradicar enfermedades, responder a la penetración de patógenos e indemnizar a los ganaderos por sus pérdidas debidas a programas de erradicación. El control eficaz de las fronteras y los programas nacionales de preparación dependen de que el gobierno y la industria trabajen conjuntamente en un proceso cuyos costos deben sufragar los responsables a través de "cuotas de usuarios". Las indemnizaciones que perciban los ganaderos por los animales sacrificados durante un brote deben ser cubiertas por aseguradoras privadas. El gobierno y la industria deben compartir el costo de la aplicación de un sistema eficaz de vigilancia, diagnóstico y respuesta. Dicho sistema debe

servir para conocer en tiempo real o casi real la situación sanitaria en todo momento y lugar, y los diversos organismos y colectivos afectados, tanto del país como del extranjero, deben tener acceso a él por Internet. Es preciso renunciar a las tradicionales medidas de respuesta porque alientan el terrorismo, y también modernizar los procesos reglamentarios de aprobación porque en su estado actual quedan rápidamente obsoletos por la evolución de la tecnología.

Palabras clave

Detección y respuesta ante un agente peligroso — Enfermedad transfronteriza — Nueva tecnología — Patógeno especialmente peligroso — Política de sacrificios — Reacción en cadena de la polimerasa — Responsabilidad — Seguro contra brotes — Sistema electrónico de notificación de enfermedades — Sistema de mando, control y comunicación — Vacunación — Vigilancia.

References

- 1. Breeze R.G. (2004). Agroterrorism: betting far more than the farm. *J. Biosecurity and Bioterrorism*, **2**, 251-264. Available at: http://www.liebertonline.com/toc/bsp/2/4;jsessionid=oP3 WwCUA6pUd.
- Briese T., Palacios G., Kokoris M., Jabado O., Liu Z., Renwick N., Kapoor V., Casas I. et al. (2005). – Diagnostic system for rapid and sensitive differential detection of pathogens. Emerg. infect. Dis., 11 (2), 310-313.
- 3. Callahan J.D., Brown F., Osorio F.A., Sur, J.H., Kramer E., Long G.W., Lubroth J., Ellis S.J. et al. (2002). Use of a portable real-time reverse transcriptase-polymerase chain reaction assay for rapid detection of foot-and-mouth disease virus. J. Am. vet. med. Assoc., 220 (11), 1636-1642.
- Delgado C., Rosegrant M., Steinfeld H., Ehui S. & Courbois C. (1999). Livestock to 2020: the next food revolution. Food, Agriculture and the Environment Discussion Paper 28. International Food Policy Research Institute. Available at: http://www.ifpri.org/2020/dp/dp28.pdf.
- European Food Safety Agency (2006). Risk assessment on foot and mouth disease. Report of the Scientific Panel on animal health and welfare. Europe. Food Safety J., 313, 1-34.
- Federal Inter-agency Working Group (2003). Animal disease risk assessment, prevention and control act of 2001. Report of PL107-9. Available at: bioengr.ag.utk.edu/eden/ pubs/USDA/AnimalDiseaseRiskAssessmentReport.pdf (accessed on 30 April 2006).

- King D.P., Ferris N.P., Shaw A.E., Reid S.M., Hutchings G.H., Giuffre A.C., Robida J.M., Callahan J.D. et al. (2006). – Detection of foot-and-mouth disease virus: comparative diagnostic sensitivity of two independent real-time reverse transcription-polymerase chain reaction assays. J. vet. diagn. Invest., 18 (1), 93-97.
- Krause P., Loescher M.S., Schroeder C. & Thomas C.W. (2000). – Proteus: insights from 2020. Copernicus Institute Press, Utrecht.
- Nerlich B., Hamilton C.A. & Rowe V. (2002). Conceptualising foot and mouth disease: the socio-cultural role of metaphors, frames and narratives. Available at: www.metaphorik.de/02/nerlich (accessed on 30 April 2006).
- Palacios G., Briese T., Kapoor V., Jabado O., Liu Z., Venter M., Zhai J., Renwick N. ct al. (2006). – Mass tag polymerase chain reaction for differential diagnosis of viral hemorrhagic fevers. Emerg. infect. Dis., 12, 693-695.